AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph beginning at page 11, line 11 with the following amended paragraph:

Figure 9 illustrates a structural alignment of a number of cytokines and interferon α-2b sequences (SEQ ID NO: 1 (IFN-α2b)); SEQ ID NO: 196 (IFN-β); SEQ ID NO: 201 (EPO); and SEQ ID NO: 210 (G-CSF)). Bold underlined residues define the region on each cytokine sequence that based on structural homology comparison corresponds to the structurally-related mutations found on the LEADs for protease resistance of IFNα-2b.

Please replace the paragraph beginning at page 11, line 29 with the following amended paragraph:

Figure 12 (A) shows a representative number of the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interferon β (corresponding to SEQ ID Nos: 233-289, 989-1015, and 1016-1302) compared to the wild-type sequence (SEQ ID NO: 196), based on 3D-scanning (structural homology method), including PAM250 analysis.

Please replace the paragraph beginning at page 12, line 3 with the following amended paragraph:

Figure 12 (B) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interferon gamma (corresponding to SEQ ID Nos: 290-311) compared to residues 1-100 of the wild-type sequence (SEQ ID NO: 199), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 7 with the following amended paragraph:

Figure 12 (C) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-10 (corresponding to SEQ ID Nos: 312-361) compared to residues 1-100 of the wild-type sequence (SEQ ID NO: 200), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 11 with the following amended paragraph:

Figure 12 (D) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of ciliary neurotrophic factor (corresponding

to SEQ ID Nos: 684-728) compared to residues 51-188 of the wild-type sequence (SEQ ID NO: 212), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 15 with the following amended paragraph:

Figure 12 (E) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of granulocyte-colony stimulating factor (corresponding to SEQ ID Nos: 631-662) compared to residues 51-177 of the wild-type sequence (SEQ ID NO: 210), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 19 with the following amended paragraph:

Figure 12 (F) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of human growth hormone (corresponding to SEQ ID Nos: 850-895) compared to residues 51-191 of the wild-type sequence (SEQ ID NO: 216), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 23 with the following amended paragraph:

Figure 12 (G) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-12 (corresponding to SEQ ID Nos: 794-849) compared to residues 51-197 of the wild-type sequence (SEQ ID NO: 215), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 12, line 27 with the following amended paragraph:

Figure 12 (H) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-6 (corresponding to SEQ ID Nos: 896-939) compared to residues 51-183 of the wild-type sequence (SEQ ID NO: 217), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 1 with the following amended paragraph:

Figure 12 (I) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of leptin (corresponding to SEQ ID Nos:

663-683) compared to the wild-type sequence (SEQ ID NO: 211), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 5 with the following amended paragraph:

Figure 12 (J) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of leukemia inhibitory factor (corresponding to SEQ ID Nos: 729-760) compared to residues 51-180 of the wild-type sequence (SEQ ID NO: 213), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 9 with the following amended paragraph:

Figure 12 (K) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of oncostatin M (corresponding to SEQ ID Nos: 761-793) compared to residues 51-150 of the wild-type sequence (SEQ ID NO: 214), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 13 with the following amended paragraph:

Figure 12 (L) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of erythropoietin (corresponding to SEQ ID Nos: 940-977) compared to the wild-type sequence (SEQ ID NO: 201), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 17 with the following amended paragraph:

Figure 12 (M) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of Flt3 ligand (corresponding to SEQ ID Nos: 401-428) compared to residues 1-100 of the wild-type sequence (SEQ ID NO: 203), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 21 with the following amended paragraph:

Figure 12 (N) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of granulocyte-macrophage colony-

stimulating factor (corresponding to SEQ ID Nos: 362-400) compared to the wild-type sequence (SEQ ID NO: 202), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 25 with the following amended paragraph:

Figure 12 (O) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-13 (corresponding to SEQ ID Nos: 603-630) compared to the wild-type sequence (SEQ ID NO: 209), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 13, line 29 with the following amended paragraph:

Figure 12 (P) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-2 (corresponding to SEQ ID Nos: 429-476) compared to the wild-type sequence (SEQ ID NO: 204), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 14, line 3 with the following amended paragraph:

Figure 12 (Q) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-3 (corresponding to SEQ ID Nos: 477-498) compared to the wild-type sequence (SEQ ID NO: 205), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 14, line 7 with the following amended paragraph:

Figure 12 (R) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-4 (corresponding to SEQ ID Nos: 543-567) compared to the wild-type sequence (SEQ ID NO: 207), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 14, line 11 with the following amended paragraph:

Figure 12 (S) shows the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of interleukin-5 (corresponding to SEQ ID

Nos: 568-602) compared to the wild-type sequence (SEQ ID NO: 208), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 14, line 15 with the following amended paragraph:

Figure 12 (T) displays the is-HIT residue positions and type of replacing amino acids selected to generate modified protein sequences of stem cell factor (corresponding to SEQ ID Nos: 499-542) compared to residues 1-141 of the wild-type sequence (SEQ ID NO: 206), based on structural homology and PAM250 analysis.

Please replace the paragraph beginning at page 61, line 3 with the following amended paragraph:

As set forth in Example 2, the 3-dimensional structure of IFNα-2b obtained from the NMR structure of IFNα-2a (PDB code 1ITF) was used to select only those residues exposed to solvent from a list of residues along the IFNα-2b and IFNα-2a sequence which can be recognized as a substrate for different enzymes present in the serum. Residue 1 corresponds to the first residue of the mature peptide IFNα-2b (SEQ ID NO:1) encoded by nucleotides 580-1074 of sequence accession No. J00207~~, SEQ ID NO:1~~. Using this approach, the following 42 amino acid target positions were identified as is-HITs on IFNα-2b or IFNα-2a, which numbering is that of the mature protein (SEQ ID NO:1 or SEQ ID NO:182, respectively): L3, P4, R12, R13, M16, R22, K23 or R23, F27, L30, K31, R33, E41, K49, E58, K70, E78, K83, Y89, E96, E107, P109, L110, M111, E113, L117, R120, K121, R125, L128, K131, E132, K133, K134, Y135, P137, M148, R149, E159, L161, R162, K164, and E165. Each of these positions was replaced by residues defined as compatible by the substitution matrix PAM250 while at the same time not generating any new substrates for proteases. For these 42 is-HITs, the residue substitutions determined by PAM250 analysis were as follows:

Please replace the paragraph beginning at page 64, line 16 with the following amended paragraph:

Also provided herein are modified IFNα-2b or IFNα-2a cytokines selected from among proteins comprising one or more single amino acid replacements in SEQ ID NOS:1 or 182, corresponding to the replacement of: N by D at position 45 ~~(e.g., SEQ ID NO:978)~~; D by G at position 94 ~~(e.g, SEQ ID NO:979)~~; G by R at position 102 ~~(e.g., SEQ ID NO:980)~~; A

by G at position 139 ~~(e.g., SEQ ID NO:981)~~; or any combination thereof. These particular proteins have also been found herein to have increased resistance to proteolysis.

Please delete the following paragraph beginning at page 89, line 26 to page 89, line 31:

A modified IFNβ-1 cytokine, comprising mutations ... of the native amino acid residue(s).

Please delete the following paragraph beginning at page 90, line 1 to page 90, line 6:

A modified IFNβ-2a cytokine, comprising mutations ... of the native amino acid residue(s).

Please replace the 7th row of Table 3 on page 142 of the specification with the following amended row:

c37-39	[[147]]	G37N/P39S	147	G37N/P39T

Please replace the paragraph beginning at page 148, line 14 of the specification with the following amended paragraph:

Four mutants with mutations ~~to additional~~ in addition to those selected by ~~the~~ rational mutagenesis were generated in the *E. coli* MutS strain and were detected by sequencing. The mutants were the following: E41Q/ D94G ~~SEQ.ID No. 199~~; L117V/ A139G ~~SEQ.ID No. 204~~; E41H/ Y89H/ N45D ~~SEQ.ID No. 198~~; and K121Q/ P109A/ K133Q/ G102R ~~SEQ.ID No. 204~~.